REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-2, 7-20, 24-28 and 31-37 are pending. Claims 16-20 and 24-28 were withdrawn from consideration by the Examiner as directed to non-elected inventions. Their rejoinder and examination in this application after allowance of an elected claim are requested.

Applicants envision that a Rule 132 declaration containing evidence that reporter groups other than acrylodan attached to glucose binding protein (GBP) would provide a biosensor with unexpected properties (e.g., weaker Kd for ligand) will be submitted in the near future. Since this would overcome a finding of prima facie obviousness, the Examiner is requested to consider such evidence before taking action on this application. Otherwise, an interview with the Examiner is requested to discuss evidence of secondary factors favoring patentability of Applicants' claimed invention.

Double Patenting

Claims 1-2, 7-15 and 31-32 were rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-8 of Patent 6,277,627 (the '627 patent). Applicants traverse for the reasons of record.

The pending claims are directed to a glucose binding protein with at least one reporter group attached at one or more of positions of 10, 93 or 183. The mutations recited in claim 12 of the '627 patent were not made to attach a reporter group. The Examiner alleged that "the cited patented claims encompass all possible attachment positions within the GBP and the disclosure of the cited patent contemplates the same."

But the attachment at position 10, 93 or 183 required in the present claims is a difference between Applicants' claimed invention and the prior art that the Examiner fails to specifically address. Here, assuming for the sake of argument that the '627 patent contemplated attachment at any position within the GBP, the Examiner still fails to identify a reason to select positions 10, 93 and 183 for attachment as required by the present claims. Further, the Examiner provided no evidence that there was a reasonable expectation of success to attach a reporter group at any position within GBP such

that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as required by the present claims. On both grounds, a prima facie case of obviousness was not established. Therefore, it would not have been obvious to attach a reporter group at one or more positions of 10, 93 or 183 within GBP.

Applicants submit that this rejection is substantially the same as the obviousness rejection under Section 103. Therefore, withdrawal of one rejection requires withdrawal of both rejections.

Claims 1-2 and 7-14 were provisionally rejected under Section 101 as allegedly claiming the same invention as that of claims 1-2 and 7-14 of copending Application No. 11/785,591. Applicants traverse because conflicting claims will be canceled upon an indication of allowability.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of

prior art elements according to their established functions." Id. at 1396. But a claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-2, 7-15 and 31-32 were rejected under Section 103(a) as allegedly unpatentable over Hellinga et al. (WO 99/34212 or US 6,277,627). Claims 1 and 73-15 were also rejected under Section 103(a) as allegedly unpatentable over Amiss et al. (US 2003/01344346 or US 6,855,556). Applicants traverse all four rejections for the same reasons explained below.

Applicants' present claims are directed to a glucose binding protein (GBP) with at least one reporter group attached at one or more of positions of 10, 93 or 183. See Table 5 at pages 33-34 and 35 of the present specification. Neither Hellinga nor Amiss teaches or renders obvious these specific positions within a GBP for attaching reporter groups. Further, there is no reason provided in the Action for why one of ordinary skill in the art would have attached one or more reporter groups at these specific positions within a GBP. The ΔI_{std} and ΔR_{max} properties of the biosensors were experimentally determined by Applicants.

In particular, attaching a reporter group at amino acid position 183 provides the unexpected results of decreased binding affinity for glucose and increased fluorescence characteristics. For a person afflicted by diabetes, a biosensor tuned to physiological concentrations of glucose in the millimolar range is a clear advantage, which is taught at page 53, lines 11-20, of the specification. As shown in Table 5, decreased binding affinity is achieved by attaching a reporter group at position 183 of glucose binding protein. See page 35 of the specification. In Table 5, it can also be seen that the fluorescence characteristics ΔI_{std} and ΔR_{max} are desirable. Fig. 5A shows that fluorescence response to log concentrations of glucose is linear. By ratiometry, clinically relevant ranges of glucose may be measured and different clinical states easily distinguished as shown in Fig. 8A. These unexpected results are not taught or rendered obvious by the prior art of record. Further, there is no reasonable expectation of success found in the cited docu-

ments to attach a reporter group at position 10, 93 or 183 of GBP such that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as recited in the present claims.

The Examiner alleged that the ΔI_{std} and ΔR_{max} properties of Hellinga's and Amiss' biosensors would necessarily be the same because "biosensors disclosed by [Hellinga and Amiss] and those of the instant invention are the same." This allegation is incorrect. These are not Section 102 rejections. Thus, the biosensors of the cited documents are clearly not the same as the presently claimed biosensors. There is no other basis in the Office Action for assuming the ΔI_{std} and ΔR_{max} properties required by claims 11-14 are inherent in the biosensors disclosed in Hellinga and Amiss because they are necessarily different as compared to the presently claimed biosensors.

The Examiner also provided no evidence that there was a reasonable expectation of success to attach a reporter group at any position within GBP such that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as required by the present claims.

Therefore, lacking both an acceptable reason for attaching a reporter group at specific positions within GBP and a reasonable expectation of success that they would be suitable as biosensors, a prima facie case of obviousness was not established by the Examiner. Withdrawal of the Section 103 rejections is requested.

35 U.S.C. 112 – Definiteness

Claims 1-2, 7-15 and 31-32 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The term "position" refers to the amino acid sequence of the bPBP. The '627 patent is cited for describing *E. coli* periplasmic binding proteins, including the amino acid sequence of glucose binding protein (GBP), on page 2, lines 3-6, of the present specification. Its contents are incorporated by reference on page 57, lines 11-14, of the present specification. A specification need not teach, and preferably omits, what is well

known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

No specific reference to a sequence identifier is required because the GBP's are known in the art. The recitation of GBP's amino acid sequence is also not necessary because numbering of their positions is well known in the art and would be understood by the skilled artisan. For example, recitation of GBP's amino acid sequence was not required for the Examiner to thoroughly search the subject matter of the claims.

Withdrawal of the Section 112 rejection is requested.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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